REMARKS

Claims 2-7 and 9 are pending in the instant application, all of which remain rejected under 35 USC § 112, first paragraph, for lack of enablement. Entry of the foregoing remarks into the record of the above identified application is respectfully requested. Applicants believe that the remarks made herein place all pending claims in condition for allowance.

THE REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, FOR LACK OF ENABLEMENT SHOULD BE WITHDRAWN

A. Claims 2-3.

Claims 2-3 are rejected under 35 U.S.C. § 112, first paragraph. The Examiner contends that claims 2 and 3 are enabled for *normal, damaged or injured central nervous system tissue* in a mammal, *wherein the damage or injury is caused by blunt trauma, stroke, or cerebral hypoxia-ischemia* but the claimed methods are not enabled for the full scope of enhancing the function of *damaged or injured central nervous system tissue* in general. The Examiner contends that Applicants support for enhancement of function, *i.e.* associative learning/cognitive function, in several instances of damaged/injured tissue is not supportive of a genus of "unlimited number" of conditions and diseases with damaged/injured excitable tissue and poor associative learning/memory.

Applicants respectfully disagree. Previously Applicants invited the Examiner's attention to the various studies published subsequent to the filing date of the present application that demonstrated that the claimed methods are enabled: 1) Lu *et al.,* 2005, Journal of Neurotrauma

22(9):1011-1017 ("Lu") (Reference FF); 2) Mogensen *et al.*, 2004, Pharmacology, Biochemistry and behavior 77:381-390 ("Mogensen ") (Reference FG); 3) Kumral *et al.*, 2004, Behavioral Brain Res. 153:77-86 ("Kumral") (Reference FH); and 4) Ehrenreich *et al.*, Molecular Psychiatry (2003), 1-13 ("Ehrenreich") (Reference FI). These references enabled the use of the current methods for damaged or injured tissue resulting from a variety of conditions: trauma, surgical trauma, cerebral hypoxia-ischemia, and schizophrenia, respectively.

Applicants respectfully disagree with the Examiner's assessment of Ehrenreich. In particular, the Examiner dismissed the Ehrenreich reference based on Ehrenreich's representation that "there is no satisfying animal model for schizophrenia that would allow sufficient prediction of the efficacy of neuroprotective treatment in man," pg. 2, col. 1, and that the condition taste aversion assay ("CTA") disclosed within Ehrenreich does not encompass injured or damaged excitable tissue. Thus, the Examiner concluded that the reference does not demonstrate that the current claims are enabled for use within neuropsychologic disorders such as schizophrenia.

However, the stated purpose of the Ehrenreich reference is to determine whether EPO satisfied certain pre-requisites that would create a basis for its use as an add-on strategy for the treatment of schizophrenia. Ehrenreich utilized the results of rodent studies, primary hippocampal neurons in culture, immunohistochemical analysis of human post mortem brain tissue and nuclear imaging technology to demonstrate that these pre-requisites were met by EPO. Namely, Ehrenreich established that 1) the peripherally administered rhEPO crosses the blood brain barrier, 2) rhEPO is enriched intracranially in healthy men and to a greater extent in schizophrenic patients, 3) EPO receptors are densely expressed in the hippocampus and cortex of schizophrenic patients and less so

in controls, and 4) peripherally administered EPO enhances cognitive function in mice in the context of a taste aversion task involving the cortical and subcortical pathways presumably affected in schizophrenia (*See* Ehrenreich, pg. 2, col. 1 & Example 2 in current application). As noted within Ehrenreich, CTA involves the brain at a variety of cortical and subcortical levels some of which may overlap with psychotic symptoms such as those related to schizophrenia. Ehrenreich, pg. 2, col. 1. Thus, even though the CTA is performed on normal rats, Ehrenreich concludes that "[t]he positive results obtained with rhEPO in this context [CTA] encourage pilot trials of rhEPO in schizophrenia since comparable properties are thought to be affected in this disease." Ehrenreich, pg. 10, col. 1. Furthermore, Ehrenreich implies that the successful use of EPO within a treatment trial in stroke patients is indicative of its utility in addressing schizophrenia. Specifically, Ehrenreich recognizes that ischemia as an acute indication and schizophrenia as a chronic indication do not compare with respect to etiology and pathogenesis; however, Ehrenreich indicates that there are some final pathways shared by the diseases, such as metabolic distress and/or lack of trophic intercellular support that would benefit from EPO's neuroprotective qualities. Ehrenreich, pg. 2, col. 2. Based on these observations, Ehrenreich concluded that EPO presented an opportunity for add-on treatment for schizophrenia and other human diseases characterized by a decline in cognitive performance and in fact indicated that a proof-of-concept trial of EPO in schizophrenia had been initiated. Ehrenreich, pg. 12, col. 1.

Applicants also invite the Examiner's attention to an additional study published subsequent to the filing date of the present application that further emphasizes that the claimed methods are enabled across a broader spectrum of indications: (1) Miu *et al.*, 2004, Behavioral Brain Research 155: 223-

229 ("Miu") (Reference FL).

Miu shows that EPO significantly improved fear conditioning performance after functional inactivation of the amygdala. In this particular study, an excitotoxic dose of glutamate was infused into the lateral nucleus of the amygdala to block the output projections to brainstem areas that control the expression of conditioned fear responses. In particular, 28 adult Wistar rats were used within the study. After being anesthetized and placed in a stereotaxis frame a bilateral lesion was produced by injecting 50 μm of L-glutamic acid with a 10 μm Hamilton syringe placed just above the lateral nucleus of the amygdala. The animals were randomly assigned to four groups. The two experimental groups received the injection of L-glutamic acid alone or with 2.5 U of recombinant EPO, and two control groups received either 10 μl saline or 2.5 U of recombinant EPO. Subsequently, the rats were subjected to trace fear conditioning to evaluate the long term and short term memory of fear responses to a tone conditioned stimulus. The rats were fear conditioned in a red Plexiglas rodent conditioning chamber with a metal grid floor, dimly illuminated and sound proof. The testing for tone conditioning took place in a blue Plexiglas chamber. After being habituated to the conditioning and testing chambers, the rats were conditioned with five pairings of a 20 s tone conditioned stimulus (CS) that co-terminated with a foot shock conditioned stimulus. The intertrial intervals varied randomly from 60 s to 90 s. Either 1 or 24 hours following the fear conditioning, the rat's response to conditioned tone were measured to determine the short and long term memory or fear response, respectively. The rats conditioning to tone and context were separately evaluated. First, after acclimating to the test chamber the rat was subjected to five tones with the same features and duration as on the previous conditioning session. Then, the rats were

placed in the conditioning chamber and given 5 minutes to acclimate after which a blind experimenter recorded the freezing time that occurred over the next 30 minutes. In both instances, the amount of time the animal engaged in freezing behavior was recorded.

Miu noted that the performance of the recombinant EPO treated group was improved in comparison to the EPO control group in the tone conditioning experiments. Applicants acknowledge that Miu taught the direct infusion of EPO as opposed to peripheral administration of EPO, but contend that one of ordinary skill in the art of a would have a reasonable expectation of achieving the same results using peripherally administered EPO in accordance with the teachings of the current application. *See also* Juul et al. *Acta Paediatr Suppl* 438: 36-42. 2002.

Thus, Applicants assert that the various references presented to the Examiner have established that EPO can enhance the associative learning, memory, or cognitive function related to numerous injuries resulting from trauma, such as blunt (Lu) or surgical trauma (Mogesen), toxins (Miu), hypoxia-ischemia (Kumral), schizophrenia and cognitive dysfunction (Ehrenreich), or stroke (Ehrenreich). Given the breadth of these disclosures, it is clear that the claims are enabled for their current scope.

B. Claim 4.

Claim 4 is rejected under 35 U.S.C. § 112, first paragraph. The Examiner contends that Claim 4 is enabled for enhancing the function of *normal, damaged or injured excitable tissue* in a mammal, *wherein the excitable tissue is central nervous system tissue* but the claimed methods are not enabled for the full scope of enhancing the function of *damaged or injured excitable tissue* wherein the *excitable tissue is central nervous system tissue or peripheral nervous system tissue.*

Applicants respectfully disagree. Specifically, Keswani teaches that systemic EPO enhances the function of peripheral nervous system tissue, sensory axons and Schwann cells, subjected to peripheral neuropathies and other neurodegenerative diseases. Keswani used an assay for peripheral neuropathy involving acrylamide to demonstrate that EPO treated animals had both an improved mechanical hyperalgesia on von Frey filament testing and greater grip strength. Keswani, pg. 822 and Figs. 5 (b) and (d). Thus, Keswani demonstrated to one of ordinary skill in the art that the peripheral administration of effective doses of EPO effectively enhanced the function of damaged excitable peripheral nervous system tissue.

Thus, Applicants respectfully maintain that Claim 4 is enabled for both central and peripheral nervous system tissues.

C. Claims 5-7 and 9.

Claims 5-7 and 9 are rejected under 35 U.S.C. § 112, first paragraph. The Examiner contends that claims 5-7 and 9 are enabled for *normal, damaged or injured excitable tissue* in a mammal, *wherein the damage or injury is caused by diabetic neuropathy or myocardial infarction* but the claimed methods are not enabled for the full scope of enhancing the function of *damaged or injured excitable tissue* in general. The Examiner contends that enhanced function of injured or damaged tissue has only been demonstrated in certain animal models and therefore contends that the scope of the claims should be limited to damage or injury caused by diabetic neuropathy or myocardial infarction.

Applicants respectfully disagree. Initially, Applicants believe that the Examiner's assessment is overly restrictive given that in the Office Action dated April 5, 2005 the examiner indicated that

the claims were enabled for stroke and autoimmune encephalomyelitis in addition to diabetic neuropathy. Further, as Applicants noted above, the art presented to date has established that the claims are also enabled for enhancing the function of excitable tissues injured or damaged as a result of blunt trauma, surgical trauma, cerebral hypoxia/ischemia, and schizophrenia. Given the scope of the enabled conditions, Applicants contend that one of ordinary skill in the art would have a reasonable expectation that the peripheral administration of EPO to a mammal with injured or damaged excitable tissue would result in the enhancement of function of that excitable tissue. This assertion is further supported by the disclosure of these references supporting the broad applicability of peripherally administered EPO. For example, Keswani suggests that recombinant EPO would be therapeutically useful in peripheral neuropathies, such as diabetic sensorimotor polyneuropathy, HIV associated sensory neuropathy, or toxic neuropathies, and other neurodegenerative diseases, such as multiple sclerosis, where dying-back axonal degeneration is a characteristic feature. Pg. 815, col. 2, - 816, col. 1. *See also* pgs. 824, col. 2-825, col. 1. Also Ehrenreich noted that "[i]n animal models, EPO has been able to improve the outcome in both acute and chronic disorders. The conditions tested range from various animal models of cerebral ischemia/hypoxia and neurotrauma to epilepsy, Parkinson syndrome or experimental autoimmune encephalitis." Based on those observations and Ehrenreich's evaluation of EPO for schizophrenia, Ehrenreich asserts that "EPO [is] an interesting compound for neuroprotective add-on strategies in schizophrenia and other human diseases characterized by a decline in cognitive performance." Pg. 12.

Additionally, Applicants invite the Examiner's attention to the additional studies published subsequent to the filing date of the present application that demonstrated that the claimed methods are

enabled: (1) Strum *et al.*, European Journal of Clinical Investigation (2005) 35, 711-717 ("Strum") (Reference FM); and (2) Erbayraktar *et al.*, submitted to *Molecular Medicine* and online before press July 10, 2006 at www.molmed.org ("Erbayraktar")(Reference FN).

Sturm demonstrates that the administration of recombinant EPO enhances the production of frataxin in *in vitro* studies suggesting the *in vivo* applicability of recombinant EPO as a means of treating Friedrich's ataxia, a neurodegenerative disorder caused by decreased expression of frataxin. Frierich's ataxia is presently an untreatable neurodegenerative disease characterized by multiple symptoms of progressive gait and limb ataxia, dysarthria, diabetes mellitus and hypertrophic cardiomyopathy. Sturm attempted to determine whether recombinant EPO could enhance the production of frataxin in cells *in vitro*. Sturm evaluated three cell types: (1) isolated lymphocytes from Freidrich's ataxia patients, (2) isolated human cardiac cells (fibroblasts and myocytes) from patients undergoing heart transplantation, and (3) P19 mouse cells (neuronal typ). Each of the cell types were incubated with EPO for a period of time at different concentrations: lymphocytes (24 hrs at 1.1, 3.3, or 9.9 U ml^{-1} recombinant EPO); cardiac cells (48 hrs at 3.3, 6.6, or 9.9 U ml^{-1} recombinant EPO); or neuronal cells (1, 24 or 48 hrs at 6.6 or 9.9 U ml^{-1} recombinant EPO). After which, the cells were lysed and an immunoblot assay was performed for frataxin. In each of the cell types treated with recombinant EPO expression of frataxin increased in a dose dependent manner. *See* pg. 713-715, Figs 1-4. It was even demonstrated that the increased expression of frataxin occurred when the exposure was limited to 1 hour. *See* Fig. 4. In addition, Strum correlated these *in vitro* results with *in vivo* observations of the frataxin-expression levels in the lymphocytes obtained from haemodialysis patients (renal failure) undergoing recombinant EPO treatment where a three-fold

increase in frataxin was observed in the lymphocytes 48 hours after receiving recombinant EPO (3000 to 10000 U). Strum then concludes that these results "provide the scientific basis for the examination of this agent for the treatment of Freidrich's Ataxia," pg. 716, and alludes to the fact that the increased expression of frataxin may provide a suitable means to prevent/ treat cardiomyopathy or treat central nervous system tissues subject to insults such as ischemia/hypoxia, trauma, immune-mediated inflammation, and excessive neuronal excitation. *See* pg. 715. Thus, Strum demonstrates EPO's ability to enhance frataxin expression in normal and injured/diseased cells.

Further, Erbayaktar demonstrates that carbamylated erythropoietin (CEPO), a non-erythropoietic form of erythropoietin further disclosed in co-pending application 10/185,841, is able to improve functional outcomes in adult rats subjected to necrotizing doses of gamma irradiation. Specifically, Erbayraktar notes that gamma knife radiosurgery is emerging as a non-invasive means of addressing brain tumors and vascular malformations but results in a cascade of acute and chronic injury. Erbayraktar evaluated the ability of CEPO to address these adverse side effects of gamma knife radiosurgery. In this assay, male Sprague-Dawley rats were randomly separated into three groups of six animals each, one acted as a control and the other groups received normal saline or 50 μg/kg of CEPO ip at the following time points: 24 hours prior to irradiation, following irradiation and daily for the 9 days following. Each of the experimental rats was administered 100 Gray to the maximal dose point in the right striatum stereotactically. The motor function of the animals was evaluated using neurological tests performed on the dosing days, day 17, and day 24. These neurological tests consisted of forelimb asymmetry use (evaluation of forelimb use in exploratory behavior), vibrissae-elicited limb placement (ability of rats to place forelimb on surface in response to

stimulation of the vibrissae), and forelimb akinesia (ability of rat to support its weight using one forelimb). Erbayraktar noted that both experimental groups initially exhibited abnormal behavior in the neurological tests with the deficits being most pronounced in the vibrissae and forelimb tests. But that the CEPO treated animals showed marked improvement in the motor function as testing progressed. *See* figures 3 and 4. Thus, Erbayraktar demonstrates that the systemic administration of CEPO enhances motor function in excitable tissues injured or damaged due to radiation, and one of ordinary skill in the art would expect that erythropoietin would also enhance the function of excitable tissues in this indication.

The experimental results described above demonstrate the efficacy of the claimed methods in animal models, and in human subjects, for a number of different conditions involving both normal excitable tissue as well as excitable tissue damaged or injured as a result of various diseases. Thus the claims are enabled and the rejection under 35 U.S.C § 112 should be withdrawn.

CONCLUSION

Entry of the foregoing remarks into the record of the above identified application is respectfully requested. Applicants estimate that the remarks made herein place the pending claims in condition for allowance. If any issues remain in connection herewith, the Examiner is respectfully invited to telephone the undersigned to discuss the same.

Respectfully submitted,

Date: July 10, 2006

By: Fred J. Hamble 42,623
Frederick J. Hamble (Reg. No.)

712 Kitchawan Road
Ossining, NY 10562
(914) 762-7586